REMARKS

This Reply is responsive to the non-final Office Action dated August 7, 2006. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.112 is respectfully requested.

I. Status of the Claims

Claims 68-173 were pending in this application at the time of the Office Action dated August 7, 2006. Claims 68-106, 169 and 170 should be withdrawn from consideration pursuant to a restriction requirement. Accordingly, claims 107-168 and 171-173 are currently under examination. Applicants respectfully request that the Examiner clarify the claims under examination in the next Office Action seeing as there appears to be a discrepancy in the Office Action Summary. According to the Office Action Summary, claim 168 is both withdrawn and under examination, and claim 170 is not mentioned at all.

II. Claim Amendments

Claim 118 was amended above to correct dependency. No prohibited new matter has been added by way of this amendment.

III. Priority Determination

According to the Office Action at page 3, the priority date granted for claims 107-136, 139, 141-143 and 146-147 is 10/20/2002, the filing date of the instant application. Claims 137-140, 144-145 and 148-175 were accorded a priority date of April 19, 2000, the filing date of the priority PCT. At the outset, it is unclear how the priority determination for claim 139 can be both 10/20/2002 and 4/19/2000. Clarification is respectfully requested. Also, it is

unclear how claims 107-136, 141-143 and 146-147 can be granted a priority date of 10/20/2002, the filing date of the instant application, without also being granted priority to the PCT application, since the instant application and the PCT application have the same specification. Clarification is respectfully requested.

The Office Action acknowledges at the bottom of page 4 that "[t]he specification as filed does provide support for a multitarget partially double stranded RNA molecule and does provide support for the two double stranded portions at both termini." However, the Office Action asserts that the specification discloses at page 9, lines 5-8 that the function of the double stranded region is to keep the RNA molecule stable, and asserts that the specification fails to disclose a partially double stranded RNA molecule wherein the two different double stranded RNA sequences are substantially homologous and complementary to at least one target gene or more than one target gene (Office Action, paragraph bridging pps. 4-5). Applicants strenuously disagree.

First, the Examiner has mischaracterized the disclosure at page 9, lines 5-8. At no point in this passage or anywhere else in the specification is it asserted that the *function* of the double stranded region is to confer stability on the RNA molecule. Rather, it is clear from this passage and throughout the specification that the double stranded sequence is designed to be homologous and complementary to the target gene (see, e.g., p. 9, l. 29-30, p. 20, lines 17-19, and working examples). The section noted by the Examiner refers to the minimum number of nucleotides required to keep the double stranded region within the molecule stable, not to the use of double stranded regions in general to confer stability to the entire RNA molecule. Indeed, as stated in the very next

sentence, at page 9, lines 7-10, "ΔG defines the state of minimal external energy required to keep a *molecular configuration* stable" (with emphasis).

Second, the instant specification certainly does disclose partially double stranded RNA molecules according to the invention that are homologous and complementary to more than one target gene. At page 8, lines 19-22, the application states: "The polynucleotide sequences described herein *may employ a multitarget or polyepitope approach, e.g., encoding sequences of more than one gene of a single target pathogen or against more than one target pathogen, or other category of target desired to be silenced*" (with emphasis). Given that the application as a whole makes it clear that the double stranded region is homologous and complementary to the target, and specifically states in this passage that the constructs of the invention may target more than one gene, the application clearly discloses multitarget partially double stranded RNA molecules that are homologous and complementary to more than one target gene.

Similarly, as disclosed at page 20, lines 17-24:

> The vectors designed to produce the dsRNAs of the invention may desirably be designed to generate two or more, including a number of different dsRNAs homologous and complementary to a target sequence . . . Various means may be employed to achieve this, including autocatalytic sequences as well as sequences for cleavage to create random or predetermined splice sites."

It is clear from the reference to autocatalytic sequences and splice sites in this passage that one means for generating several different dsRNAs is to generate a single multitarget RNA encoding the separate individual double stranded RNAs and use cleavage to generate individual molecules. This process necessarily entails the formation of a single multitarget partially double stranded RNA molecule.

With reference to claim 139, the Office Action also refers to the portion of the specification that discusses preferred lengths of the disclosed RNA molecules as ranging from 100 to 10,000 polynucleotides, and asserts that the specification does not contemplate an expression vector that encodes two or more double stranded sequences each comprising 11 to 30 nucleotides. Applicants respectfully note that the length range to which the Examiner refers is only a *preferred* range for the length of the molecule *as a whole*. Indeed, the specification states, that "The 'at least partially double stranded RNA molecule' *includes* an RNA polynucleotide sequence of between about 100 to 10,000 polynucleotides in length" (with emphasis). Moreover, the specification clearly discloses at page 9, lines 5-7 that the double stranded regions *within* this molecule may be at least 11 to 30 nucleotides, and clearly discloses at page 20, lines 17-24 that a vector may be used to synthesize the single multitarget transcript, which may then be cleaved using autocatalytic sequences or other cleavage sites to generate a number of different dsRNAs homologous and complementary to a target sequence. Accordingly, the application when read as a whole certainly does disclose an expression vector that encodes two or more double stranded sequences each comprising 11 to 30 nucleotides.

Given all these remarks, Applicants believe that specific support in the instant specification has been provided for all the claimed subject matter. Given that the instant specification is identical to the disclosure of the priority PCT application, Applicants respectfully request that the Examiner reconsider the priority designation and assign a priority date of at least the PCT application fling date (4/19/2000) for all the pending claims.

IV. Claim Objections

Claims 141 and 171 were objected to as being in improper dependent form. According to the Office Action, claims 141 and 171 fail to further limit claim 137, which is drawn to an expression vector encoding two or more different double stranded RNA. Applicants respectfully traverse the objection since the vector of claim 137 can encode two or more different double stranded RNA sequences as claimed, which in one embodiment may be part of a single multitarget partially double stranded RNA molecule as recited in claims 141 and 171. As discussed above in response to the priority determination, the specification discloses at page 20, lines 17-24 that an expression vector may be used to several different double stranded molecules, which may be generated by cleavage of a single partially double stranded transcript. Reconsideration and withdrawal of the objection to claims 141 and 171 are respectfully requested.

Claim 118 and the claims dependent thereon were objected to because claim 118 is dependent on a non-elected claim. Claim 118 has been amended above to depend on claim 108. Accordingly, the objection may now be withdrawn.

V. Rejections under 35 USC §112

Claims 107-136, 139, 141-143 and 146-147 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. According to the Office Action, these claims were rejected under §112, first paragraph for the same reasons used to deny these claims priority to the parent PCT application. Applicants respectfully submit that all the arguments provided above in

response to the priority determination are equally applicable here, since the present application has the same disclosure as the parent PCT application. Accordingly, claims 107-136, 139, 141-143 and 146-147 are adequately described in the instant specification, and reconsideration of the written description rejection with respect to these claims is respectfully requested.

Claims 170-173 were rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. According to the Office Action, it is understood that the double stranded region can comprise sequences wherein one strand is homologous to a target gene and the other strand is complementary to the target gene, but it is not understood how the non-double stranded region can be both homologous and complementary to the target sequence. Applicants respectfully submit that it is clear from the language of claims 107 and 137 that it is the double stranded regions that are homologous and complementary to the target sequence, not the non-double stranded regions. Accordingly, the claim language is clear. Applicants respectfully request reconsideration of this rejection under §112, second paragraph.

VI. Prior Art Rejections

Claims 107-110, 113-116, 123-141, 144-149, 156, 163-168 and 171-173 have been rejected under 35 U.S.C. §102(a) as being anticipated by Leirdal *et al.* (2002). According to the Office Action, Leirdal *et al.* teaches a multitarget partially double stranded RNA molecule comprising two different double stranded RNA sequences that are complementary to a GFPsi1

sequence and a PKCαsi3 sequence, respectively. Applicants respectfully traverse the rejection.

Claims 137-140, 144-145 and 148-173 have been assigned a priority date of 4/19/2000. Therefore, Leirdal *et al.* cannot be prior art against these claims. Further, as Applicants have shown above in response to the priority determination, all the pending claims have support in the instant specification, which is the same as the PCT specification. Accordingly, all the other claims should be granted the priority date of the PCT application (4/19/2000), and Leirdal *et al.* is not prior art against any of the pending claims. Reconsideration and withdrawal of the rejection under §102(a) based on Leirdal *et al.* are respectfully requested.

Claims 107-148, 156-168 and 171-173 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Taira *et al.* and Fire *et al.* (US 6,506,559). According to the Office Action, Taira *et al.* teaches multitarget partially double stranded ribozymes but does not specifically teach that the double stranded regions of the ribozyme are homologous and complementary to the target gene. However, according to the Office Action, it would have been obvious to use double stranded RNAs in the construct of Taira *et al.* because Fire *et al.* allegedly teach that "double stranded RNA capable of initiating RNA interference is a more sequence specific alternative to reducing exression of a target gene than the antisense type mechanisms as taught by Taira *et al.*" (Office Action, p. 18). Applicants respectfully traverse the rejection.

Taira *et al.* teaches multitarget ribozymes not multitarget antisense constructs. While there are regions in the Taira *et al.* constructs that are antisense to the target gene transcript, a ribozyme construct does not operate by an "antisense type mechanism" *per se* as asserted in the Office Action. Rather, a ribozyme operates by binding of the antisense region to the target transcript, and subsequent cleavage of the double stranded region thus formed by the cleavage action of the ribozyme. The skilled artisan would not have been motivated to substitute a double stranded region corresponding to the target gene into the ribozyme of Taira *et al.* because if they did, the antisense region of the ribozyme would no longer be free to bind to the target transcript, and cleavage of the target transcript would not occur. Rather, it is possible that cleavage of the double stranded region included in the ribozyme could occur, destroying the ribozyme. Indeed, given that ribozymes and RNA interference operate in entirely distinct ways to accomplish inhibition of gene expression, there would have been no reason for the skilled artisan to use the double stranded RNA molecules of Fire *et al.* in the multitarget ribozymes of Taira *et al.*

In view of the above remarks, reconsideration and withdrawal of the rejection under §103(a) based on Taira *et al.* and Fire *et al.* are respectfully requested.

Claims 107-168 and 171-173 were rejected under 35 U.S.C. §103(a) as being unpatentable over Werther *et al.* (US 5,929,040), Fire *et al.* (US 6,506,559), Heifetz *et al.* (WO 99/61631) and Thompson *et al.* (US 6,146,886). According to

the Office Action, Werther *et al.* teaches a multivalent antisense molecule but does not disclose the use of double stranded RNA sequences or the expression of double stranded RNA sequences from a vector. However, the Examiner believes it would have been obvious to the skilled artisan at the time the invention was made to substitute double stranded RNA as allegedly disclosed in Fire *et al.* and Heifetz *et al.* as an alternative for the antisense sequences in the constructs of Werther and express these molecules in a vector as also disclosed in Fire *et al.* and Heifetz *et al.*. Thompson is relied up for teaching expression of therapeutic RNAs including ribozymes and antisense RNAs using a RNA polIII promoter. Applicants respectfully traverse the rejection.

The skilled artisan would not have been motivated to substitute a double stranded region that is both homologous and complementary to a target gene into the multivalent antisense molecule of Werther *et al.* because if they did, the antisense regions of Werther's multivalent molecule would no longer be free to bind to the target transcripts. Indeed, antisense RNA operates by binding directly to the complementary target gene transcript. Double stranded RNA operates by a more complex mechanism involving cleavage of the double stranded RNA by Dicer enzyme and incorporation of the cleavage products (small interfering RNAs or siRNAs) into the RNA-inducing silencing complex (RISC). RISC then cleaves and discards the passenger (sense) strand of the siRNA duplex and the remaining antisense strand of the siRNA guides RISC to the target mRNA, resulting in endonucleolytic cleavage of the target mRNA. Given that antisense RNA and double stranded RNA operate in entirely distinct ways to accomplish inhibition of

gene expression, there would have been no motivation for the skilled artisan to use the double stranded RNA molecules of Fire *et al.* or Heifetz *et al.* in the multivalent molecules of Werther *et al.*

The courts have made it clear that in putting together an obviousness rejection, the proposed modification introduced by the secondary reference cannot change the principal mode of operation taught in the primary reference. For instance, according to MPEP 2143.01, section VI:

> If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (Claims were directed to an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers inserted in a resilient sealing member. The primary reference relied upon in a rejection based on a combination of references disclosed an oil seal wherein the bore engaging portion was reinforced by a cylindrical sheet metal casing. Patentee taught the device required rigidity for operation, whereas the claimed invention required resiliency. The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.).

Thus, given that the only mechanism disclosed in Werther *et al.* for inhibiting gene expression is antisense inhibition where the antisense constructs actually bind to the target sequence, and given that the skilled artisan at the time would have expected that substituting a double stranded region that is both homologous and complementary to the target into these antisense constructs would have interfered with antisense inhibition, there would have been no motivation to use the double stranded RNAs of Fire *et al.* or Heifetz *et al.* in the

constructs of Werther *et al.* at the time the invention was made. Thompson *et al.* does nothing to change the fact that substituting the double stranded RNAs of Fire *et al.* or Heifetz *et al.* would change the basic principle under which the Werther construction was designed to operate.

The Office Action asserts in the paragraph bridging pages 21-22 that one would have been motivated to combine the references "because certain diseases are triggered by expression from similar genes and therefore co-suppression, as taught by Werther *et al.* is an effective method." Applicants fail to understand the Examiner's point here since "co-suppression" refers to the inhibition of gene expression that occurs in some instances in the presence of a sense construct rather than an antisense construct. It has nothing to do with inhibiting more than one gene at a time.

As a final matter, Applicants respectfully submit that this rejection does not appear to explain why it would have been obvious based on these references to express from a vector two or more different double stranded RNA sequences from different promoters as recited in claims 150-155. The rejection asserts that Werther *et al.* teaches a multivalent antisense structure but acknowledges that the reference does not teach expression from a vector. Fire *et al.* and Heifetz *et al.* have been cited for the premise that it would have been allegedly obvious to replace the antisense regions in the multivalent constructs of Werther with double stranded regions, and that one could express the multivalent constructs using a vector, but Applicants do not see any assertions made in the Office Action regarding obviousness of a vector

expressing two or more different double stranded RNA sequences from different promoters as recited in claims 150-155. It is clear that a proper §103 rejection must show how the prior art reference (or references when combined) teaches or suggests all the claim limitations. See MPEP 706.02(j).

In light of these remarks, reconsideration and withdrawal of the rejection under §103(a) based on Werther *et al.*, Fire *et al.*, Heifetz *et al.* and Thompson *et al.* are respectfully requested.

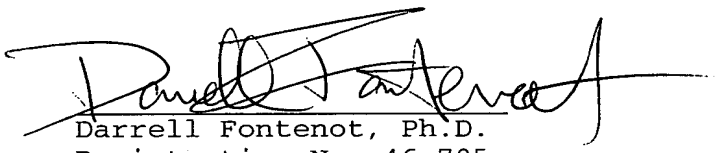
In summary, Applicants believe that this Reply adequately addresses all the objections to and rejections of the claims, and that the application should now be allowed. At the very least, Applicants respectfully request immediate notification of the allowability of claims 150-155, as there appears to have been no proper rejection made against these claims. For instance, these claims were accorded a priority date of April 19, 2000. Accordingly, these claims were correctly not included in the rejection based on Leirdal *et al.* These claims were not included in any rejection under §112, first or second paragraphs. These claims were not included in the §103(a) rejection over Taira *et al.* and Fire *et al.* Although these claims were listed by number in the §103(a) rejection based on Werther *et al.*, Fire *et al.*, Heifetz *et al.* and Thompson *et al.*, the subject matter in claims 150-155 was not addressed in the rejection. Accordingly, it appears that claims 150-155 at the very least are in condition for allowance.

This reply is fully responsive to the Office Action dated August 17, 2006. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 01-1425. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted,



Darrell Fontenot, Ph.D.
Registration No. 46,705

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
(845) 602-3144
Attorney for Applicants